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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/844,450	04/27/2001	William H. Frey II	83935	9084

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EXAMINER	
MCINTOSH III, TRAVISS C	
ART UNIT	**PAPER NUMBER**
1623	

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/844,450	FREY ET AL.	
	Examiner	Art Unit	
	Traviss C McIntosh	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-80* is/are pending in the application.

4a) Of the above claim(s) *5-31 and 45-80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 32-44* is/are rejected.

7)☒ Claim(s) *35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

The Amendment filed April 16, 2004 has been received, entered into the record, and carefully considered. The following information provided in the amendment affects the instant application by:

Claims 1, 4, and 32 have been amended.

Claims 5-31 and 45-80 are withdrawn.

Remarks drawn to rejections of Office Action mailed June 13, 2003 include:

112 1st paragraph rejections: which has been withdrawn and a new 112 1st paragraph rejection set forth.

112 2nd paragraph rejections: have been overcome in part by applicant's amendments and have been withdrawn in part.

103(a) rejection: which has been overcome by applicant's arguments and has been withdrawn.

An action on the merits of claims 1-4 and 32-44 is contained herein below. The text of those sections of Title 35, US Code which are not included in this action can be found in a prior Office action.

As a preliminary matter, the examiner would like to note that in applicant's response filed April 16, 2004, on page 21, the top paragraph drawn to "Status of the Claims", applicants state that "claims 1-4 and 32-44 (species E and associated linking claims) were elected pursuant to an

election of species requirement", however, the requirement set forth was not a species election, but a restriction between inventions. Thus, claims 1-4 and 32-44 were elected due to a restriction requirement, and not a species requirement. The only species requirement set forth was due to the use of the divergent compounds in the methods as claimed (i.e., phosphorylated compounds having (a) glycerol, (b) an amino acid, etc.).

Claim Objections

Claim 35 is objected to because of the following informalities: the claim lacks a period. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 1-4 and 32-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of protecting the muscarinic acetylcholine receptor in Alzheimer's patients from inactivation caused by oxidative stress induced by heme/peroxide or the low molecular weight inhibitor found in Alzheimer's disease patients using compounds with two or three phosphorus atoms and other known antioxidants, does not reasonably provide enablement for methods of protecting any tissue component in any subject from anything using the broad group of the compound in claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in ***In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400,***

1404 (Fed. Cir. 1988). A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:
(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims - The nature of the invention

The claims of the instant application are drawn to methods of protecting any tissue component from anything comprising administering a pyrophosphate analog with 2-900 phosphorus atoms. Dependent claims limit the protection to be from oxidative stress, the tissue component to be receptors, proteins, lipids, nucleic acids, carbohydrates, hormones, vitamins, and cofactors, the receptors to be receptors for various things, such as for any neurotransmitter, any neuropeptide, any steroid, any purine, any ion channel, etc. Dependent claims additionally limit the compound to be used to various compounds such as pyrophosphate, imidodiphosphate, etc., limits the patient to be treated to one who has various diseases, and provides methods for combination therapy with various substances.

The state of the prior art

Antioxidants are known in the art to be chemical substances that neutralize the oxidant effects of free radicals and other substances. Compounds are known in the art to have varying degrees of antioxidant activity, as set forth by the differences of the 7-methoxychromones and 7-hydroxychromones (compound #556 and feruloyl aloesin) of Yu et al (US Patent 5,939,395). Antioxidants estrogen, vitamin E and vitamin C are known to have protected muscarinic acetylcholine receptors (mAChR) from inhibition by the low molecular weight inhibitor found in Alzheimer's disease patients or hemin (Venters et al., Brain Research, 764, pp. 93-100, 1997). The art is silent to the use of the claimed compounds having 4-900 phosphorus atoms having antioxidant activity. Moreover, the art is silent to the correlation between inhibition of mAChR in Alzheimer's patients and protecting any other tissue component from anything.

The level of predictability in the art

The examiner acknowledges the probability and predictability that the active agents as set forth in claims 32 and 33 have efficacy in Alzheimer's patients in protecting mAChR inactivation caused by oxidative stress induced by heme/peroxide or the low molecular weight inhibitor found in Alzheimer's disease patients, however the art is silent with regard to the predictability of any compound as set forth by the structure of claim 1, indeed has efficacy in protecting any tissue component from anything, especially in view of the fact that Yu et al. showed a 7-hydroxychromone with such a decreased activity as compared to aloesin and aloeresin (art known antioxidants).

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance which would allow the skilled artisan to extrapolate from the disclosure and examples provided to use the claimed

method commensurate in the scope with the instant claims. There is a lack of data and examples which adequately represent the scope of claim as written. The examiner notes, there has not been provided sufficient instruction or sufficient methodological procedures to support the alleged efficacy instantly asserted using a compound from the broad group of claim 1.

The existence of working examples

The working examples set forth in the instant specification are directed to the use of various compounds in testing for protection of mAChR from inactivation caused by the low molecular weight inhibitor found in Alzheimer's patients or heme/peroxide. It is noted that there has been no combination therapy tested. The results showed that various compounds do protect a mAChR from the inhibitory effects of the endogenous LMW inhibitor and heme/peroxide, thus allowing agonist/antagonist binding to the mAChR.

However, there has not been provided sufficient evidence which would warrant the skilled artisan to accept the data and information provided in the working examples as correlative proof that any compound of claim 1 would indeed protect any tissue component from anything.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the use of any compound of claim 1 in a method of protecting any tissue component from anything without undue experimentation. One skilled in the art could not use the entire scope of the claimed invention without undue experimentation. One skilled in the art would be confronted with an undue burden of experimentation to isolate, characterize, and test the various compounds of claim 1 to determine if indeed they have efficacy as protective agents

from any number of various possibilities in various tissue components. As set forth supra, applicants have successfully shown methods of protecting the muscarinic acetylcholine receptor in Alzheimer's patients from inactivation caused by oxidative stress induced by heme/peroxide or the endogenous low molecular weight inhibitor found in Alzheimer's disease patients using compounds with two or three phosphorus atoms and other known antioxidants.

Claims 1-4 and 32-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "a **small** alkyl group" in claim 1 is a relative term which renders the claim indefinite. The term "small" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention.

Claim Rejections - 35 USC § 103

Claims 1-4 and 32-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Venters et al. (art of record) in view of Siren et al. (US Patent 5,135,923).

The claims of the instant application are drawn to methods of protecting the muscarinic acetylcholine receptor in Alzheimer's patients from inactivation caused by oxidative stress induced by heme/peroxide or the low molecular weight inhibitor found in Alzheimer's disease patients using compounds with two or three phosphorus atoms and other known antioxidants.

Venters et al. teaches that an endogenous inhibitor of antagonist binding to mAChR is reported to be three fold higher in Alzheimer's patients. Venters et al. additionally teaches that free radical scavengers Trolox and Mn^{2+}, and EDTA blocked the activity of the endogenous inhibitor and of hemin. Moreover, Venters teach that the antioxidants estrogen, vitamin E, and vitamin C all protect mAChR from inhibition by the endogenous inhibitor or hemin. Venters et al. additionally teach that these antioxidants may function to protect the integrity of the mAChR in vivo and may have therapeutic potential in AD where free heme could be the source of oxidative stress (see abstract). What is not specifically taught is to use the compounds as set forth in the instant application to protect the mAChR from inhibition by oxidative stress caused by heme/peroxidase or the endogenous LMW inhibitor in Alzheimer's patients.

Siren teaches the use of inositol triphosphate to reduce the negative effect of free radicals in tissues (see abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to protect the mAChR in Alzheimer's patients from inactivation caused by oxidative stress induced by heme/peroxide or the low molecular weight inhibitor found in Alzheimer's disease patients using the triphosphate compound inositol triphosphate as applicants have done with these references before them. Venters et al. teaches that free radical scavengers Trolox and Mn^{2+}, and EDTA blocked the activity of the endogenous inhibitor and of hemin. Moreover, Venters teach that the antioxidants estrogen, vitamin E, and vitamin C all protect mAChR from inhibition by the endogenous inhibitor or hemin. Venters et al. additionally teach that these antioxidants may function to protect the integrity of the mAChR in vivo and may have therapeutic potential in AD where free heme could be the source of oxidative stress (see abstract) and Siren teaches the

use of inositol triphosphate as an antioxidant. One would have been motivated to use the inositol triphosphate compound of Siren in the method of Venters because Venters teaches that antioxidants may function to protect the integrity of mAChR in oxidative conditions and Venters teaches that the triphosphate compounds is an effective antioxidant.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Traviss C McIntosh whose telephone number is 571-272-0657. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Traviss C. McIntosh III
August 3, 2004

James O. Wilson
Supervisory Patent Examiner
Art Unit 1623